REMARKS

Claims 1-60 were pending. The Examiner has withdrawn claims 1-2, 7, 9-22, 24-48, 50-55, 59 and 60 as drawn to non-elected inventions. Applicants have canceled claims 49, 51-55, 57 and 59-60 without prejudice and reserve the right to prosecute the subject matter of the canceled claims in one or more related applications. Applicants have amended claims 1, 3, 4, 5, 7, 9, 17, 18, 23, 32, 56 and 58 and have added new claims 61-72 to more particularly point out and distinctly claim that which the Applicants regard as the invention. The amendments and new claims are fully supported by the application as filed. Accordingly, no new matter has been added. After entry of this amendment, claims 1-50, 56, 58 and 61-72 will be pending and claims 3-6, 8, 23, 56, 58 and 61-72 will be under consideration.

Objections to the Specification

The Examiner objects to the title and abstract of the instant specification for allegedly not clearly indicating the subject matter being examined and suggests amendment to specifically mention FcγRIIB. Applicants respectfully traverse the objection.

Applicants submit that it is premature to require amendment of the title and/or abstract of the specification, in particular, to mention FcγRIIB. Fusion proteins comprising the extracellular domain of FcγRIIB were elected as a species of the fusion proteins of the invention of Group I outlined in the restriction requirement dated February 28, 2008. Because proteins comprising FcγRIIB are only a species of currently elected invention, additional species of the fusion proteins of Group I may yet be considered in accordance with the provisions of 37 C.F.R. § 1.141. Accordingly, Applicants request that the instant objection be held in abeyance until indication of allowable subject matter.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

The Examiner has rejected claims 3-6, 23, 49 and 58 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Examiner contends the specification fails to enable one of skill in the art to make or use a claimed molecule that demonstrates 0% binding to any FcγR from any species. Preliminarily, Applicants point out that claim 49 has been canceled, rendering the instant rejection moot with respect to this claim. Claim 58 has been amended to specify that the homologous polypeptide must exhibit the same ligand binding and effector activity as the identified amino acid sequence.

With respect to the remaining claims, Applicants have amended claim 3, in part, to specify that the claimed fusion protein comprises an Fc domain of a human immunoglobulin having one or more amino acid modifications, which modifications modulate Fc domain effector function. Amino acid modifications that modulate antibody effector function were well known in the art at the time of filing of the instant application, and the specification cites numerous references disclosing amino acid modifications demonstrated to modulate effector function as well as protocols for assessing the functionality of the modified Fc domains. For example, the specification incorporates by reference patent documents disclosing amino acid modifications that reduce or abrogate binding to one or more activating effector ligands (*e.g.*, FcγRIIA, FcγRIIA and/or the C1q component of complement) and/or increase binding to an inhibitory ligand (*e.g.*, FcγRIIB) in paragraphs [0024] at page 8, and [00110]-[00111] at pages 32-34. Moreover, the specification also provides a detailed teaching of additional exemplary modifications known to effect such modulation (see, *e.g.*, paragraphs [00133]-[00142] at pages 44-47 of the specification as filed). Considering the level of the skill in the art, the detailed teaching of the specification and the amount of art cited in the specification, Applicants submit that claim 3 as amended herein, and claims 4-6 and 23 as dependent thereon, are enabled throughout their full scope.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 112, First Paragraph, have been obviated or overcome and should be withdrawn.

The Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

The Examiner rejects claim 56 under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent 6,034,223 to Maddon et al. ("Maddon") and claims 56 and 57 under 35 U.S.C. § 102(b) as allegedly anticipated by international publication WO 00/32767 to Sondermann et al. ("Sondermann"). Applicants respectfully point out that claim 57 has been canceled, rendering the instant rejection moot with respect to this claim.

With respect to claim 56, the Examiner contends that use of the indefinite article "an" in a claim in reference to amino acid sequences identified by sequence identifiers (*i.e.*, SEQ ID Nos.) indicates that the claim encompasses polypeptides comprising not only the entirety of the referenced sequence(s) but also fragments thereof. The Examiner then alleges that Maddon and/or Sondermann anticipate claim 56 because these references disclose fragments of the claimed sequences.

Although not agreeing with the Examiner's position and merely to advance prosecution, Applicants have amended claim 56, in part, such that the referenced sequences are claimed using the definite article "the." Applicants submit that the amendment makes clear that the claimed polypeptides must comprise the entirety of the referenced sequence, obviating the instant rejections.

In view of the foregoing, Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

The rejections over Presta in view of Allaway

The Examiner has rejected claims 8, 56 and 57 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. patent 6,911,321 to Presta et al. ("Presta") in view of U.S. patent 5,817,767 to Allaway et al. ("Allaway"). The Examiner contends that Presta teaches hybridizing soluble Fc receptors ("FcRs") to Fc domains and that Allaway teaches the use of IgG2 domains to reduce the immunogenic potential of chimeric proteins comprising Fc domains. Applicants respectfully traverse the rejection.

Applicants have amended the independent claims such that the invention is directed to dimeric fusion proteins comprising a Fc domain of an immunoglobulin, *e.g.*, the hinge-constant region of IgG2, wherein the Fc domain comprises one or more amino acid modifications that modulate one or more effector functions of the Fc domain. Applicants submit that none of the references cited by the Examiner, either individually or in combination, render obvious the instantly claimed dimeric fusion proteins because none of the references, or combinations thereof, teach or suggest modification of the Fc domain, in particular, to modulate the effector function of the domain.

Presta presents an investigation of the differences in binding affinities among various monkey FcRs. To that end, Presta discloses the manufacture of soluble monkey FcR and teaches that heterologous proteins may be joined to the soluble FcR to aid in FcR stability, secretion or purification. In particular, Presta discloses that the soluble FcR proteins are fused to heterologous peptides such as the 6-HIS tag, FLAG tag or immunoglobulin constant domains to facilitate recombinant protein purification. However, Presta fails to teach or suggest that the immunoglobulin constant domain, *i.e.*, Fc domain, should be modified for *any* purpose, much less to modulate the effector function of the domain as instantly claimed. Moreover, Presta fails

to teach or suggest that the immunoglobulin constant domain has any utility beyond aiding purification or enhancing stability/oligomerization of the FcR and, therefore, fails to suggest that fusion proteins comprising immunoglobulin constant domains may be used as *in vivo* therapeutic moieties. Because Presta does not teach or suggest either independent modification of the Fc domain for any purpose or the *in vivo* use of molecules comprising immunoglobulin constant domains, Presta cannot render obvious the modification of such molecules to mediate their *in vivo* properties, *e.g.*, effector function. Accordingly, Presta cannot render obvious the modification of an Fc domain to modulate effector function as instantly claimed in claim 8 or a molecule exhibiting such altered effector function as claimed in claims 56 and 57. Thus, Presta fails to render obvious the molecules of the invention as instantly claimed.

Allaway does not remedy the deficiencies of Presta. As noted by the Examiner, Allaway teaches that the IgG2 Fc domain is of particular use in chimeric molecules comprising IgG Fc domains because the IgG2 Fc domain exhibits minimal allotype variability when compared to the Fc domains of other IgG isotypes. This reduces the immunogenic potential of the IgG2-Fc containing molecules when used as a therapeutic. As understood by one of skill in the art, Allaway teaches that the reduction in immunogenic potential of chimeric molecules comprising an IgG2 Fc domain arises because the particular IgG2 Fc domain is unlikely to exhibit sequence variability relative to the Fc domain of a host IgG2 molecule. In contrast, the dimeric proteins as instantly claimed comprise one or more amino acid modifications in the Fc and/or IgG2 hinge-constant domain, which modifications increase sequence variability relative to native (*i.e.*, wild-type) Fc domain amino acid sequences. Thus, Allaway teaches away from modifying Fc domains to comprise modifications relative to wild-type molecules because the reference teaches away from increasing Fc domain sequence variability relative to wild-type Fc domains of wild-type molecules. Accordingly, Allaway teaches away from the instantly claimed dimeric fusion proteins. Therefore, Allaway, whether alone or in combination with Presta, fails to render obvious the invention as instantly claimed.

The rejections over Sondermann in view of Ashkenazi and/or Allaway

The Examiner has further rejected claims 8, 56 and 57 under 35 U.S.C. § 103(a) as allegedly obvious over international publication WO 00/32767 to Sondermann et al. ("Sondermann") in view of Ashkenazi et al., 1997, *Curr. Opin. Immunol.* 9:195-200 ("Ashkenazi") and in view of Allaway. Applicants respectfully traverse the rejection.

Sondermann discloses the production and use of recombinant, soluble FcR extracellular domains, in particular, for elucidation of the residues involved in FcR-Fc interaction. Sondermann presents no disclosure whatsoever of combining the soluble FcR proteins with any heterologous proteins, *e.g.*, as fusion proteins, much less a dimeric fusion protein comprising a FcR and a Fc and/or IgG2 domain as instantly claimed. Accordingly, Sondermann fails to teach or suggest the proteins of claims 8, 56 or 57 and fails to render obvious the proteins of the invention as instantly claimed.

Ashkenazi does not remedy the deficiencies of Sondermann. Ashkenazi provides a review of the state of the art of immunoadhesins that comprise the soluble portions of non-Fc binding cell receptors, *e.g.*, that comprise the ligand binding portions of tumor necrosis factor or interleukin receptors (receptors in the "TNFR" or "IL" family, respectively). Although Ashkenazi points out that the Fc portion of the immunoadhesin can confer effector function, Ashkenazi provides no teaching or suggestion that the native effector function of the Fc portion should be modulated, much less that such modulation could be effected by modification of one or more amino acid residues in the Fc region as instantly claimed. Thus, whether alone or in combination with Sondermann, Ashkenazi fails to render obvious the dimeric fusion proteins of the instant claims.

Similarly, Allaway fails to remedy the deficiencies of Sondermann whether viewed alone or in combination with Ashkenazi. As discussed in detail above, like Ashkenazi, Allaway provides no teaching or suggestion for the modification of the Fc domain to modulate Fc effector function as instantly claimed in independent claims 3, 8, 56 and 57. Thus, Allaway, whether alone or in combination with Sondermann and/or Ashkenazi, fails to render obvious the dimeric proteins of the instant claims.

In view of the foregoing, Applicants submit that the rejections under 35 U.S.C. § 103(a) have been obviated or overcome and request that they be withdrawn.

CONCLUSION

Applicant respectfully requests that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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